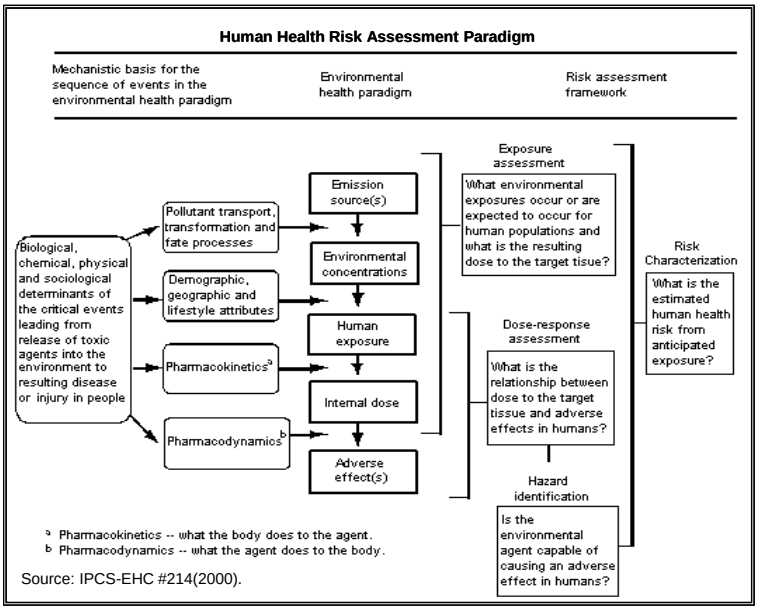
4. HUMAN HEALTH RISK ASSESSMENT FOR METALS



The National Research Council (NAS/NRC, 1996, 1994b, 1983), of the National Academy of Sciences (NAS), described four phases to the human health risk assessment paradigm (Hazard Identification, Dose-response Assessment, Exposure Assessment, and Risk Characterization) and identified risk communication as a fifth area of study. These principles have been further addressed in EPA's *Risk Characterization Handbook* (U.S. EPA, 2000c). In brief, hazard identification (referred to as "hazard characterization" in recent EPA documents) involves the determination of whether a chemical is or is not causally linked to particular health effects. Dose-response involves the determination of the relationship between the magnitude of exposure and the probability of occurrence of the health effects in question. A parallel step in the process toward the hazard identification and dose-response assessment is exposure assessment. In Exposure Assessment, the risk assessor quantifies the total exposure to a toxic agent in the environment based on amount taken into the body, including any combination of the oral, inhalation, and dermal routes of exposure. For some assessments specific to a single exposure route, exposure may be expressed as an environmental concentration (e.g., ambient air or water concentrations). Depending on the application, the exposure assessment may be specific to a site, a population at a specific location, or it may broadly cover a region or an entire nation. Risk Characterization is the final step in the NAS paradigm. In this phase, the risk assessor summarizes and interprets the information from hazard identification, dose-response, and exposure steps, often by quantitatively comparing exposures with doses that are associated with potential health effects. Risk Characterization addresses the nature and often the magnitude of the human health risks, including attendant uncertainty. These steps are addressed in greater detail in the following sections, with particular attention to the aspects specific to metals.

The information provided here complements that given by the available Agency guidance for the risk assessment process, e.g., for carcinogen risk assessment (U.S. EPA, 2005, 1986), exposure assessment (U.S. EPA, 1992c), developmental toxicity (U.S. EPA, 1991), neurotoxicity (U.S. EPA, 1998c), chemical mixtures (U.S. EPA, 2000b, 1986), and cumulative risk (U.S. EPA,

2003e), and focuses on the unique and specific characteristics of metals and metal compounds that may be applied in metals risk assessments for human health.

4.1. METALS PRINCIPLES

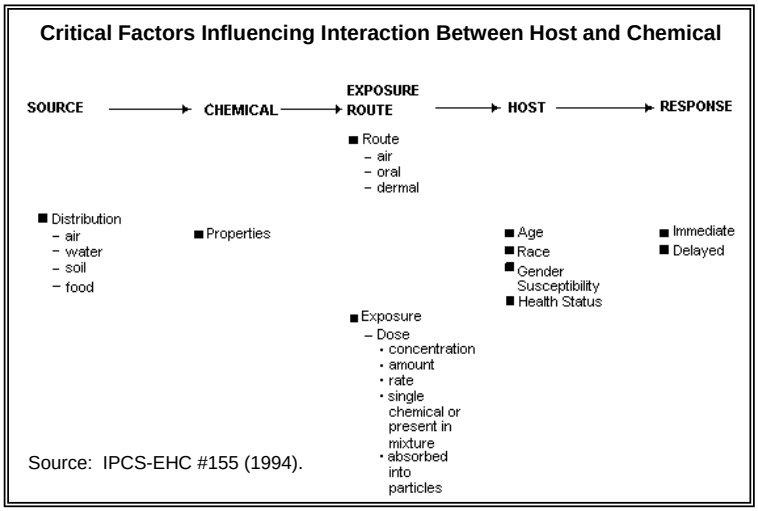
Metals are associated with a variety of health effects that are reviewed in detail in EPA's Integrated Risk Information System (IRIS) Toxicology Reviews, the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles, the World Health Organization's International Programme for Chemical Safety (WHO/IPCS) Environmental Health Criteria Documents, and metal toxicology reviews (e.g., Lukaski, 1999; Hathcock, 1996; Mertz, 1995, 1993; Wallach, 1985). Metals have specific attributes that should be considered in all risk assessments. These principles for metals risk assessment (see Chapters 1 and 2) apply in various ways to human health risk assessments, depending on the scale of the assessment (site specific, regional, or national). This section describes applications of the metals principles to human health assessments within the standard risk assessment framework. Specifically, they fall into the risk assessment paradigm as follows:

Background levels	Exposure Assessment
Mixtures	Exposure and Effects Assessment
Essentiality	Effects Assessment
Forms of metals	Exposure Assessment (bioavailability) and Effects Assessment (absorption, distribution, metabolism, and excretion [ADME] and toxicity)
Toxicokinetics/toxicodynamics	

Often times, human health risk assessors start their analysis with a metal-specific reference value (RfD/RfC) and/or cancer potency factor that has been developed through a process separate from the health risk assessment. The role of the human risk assessor is to appropriately integrate the reference values and potency factors with the exposure assessment. Thus, the risk assessor needs an understanding of the toxicological endpoints and mechanisms of action that underlie the derivation of these values to ensure that, for example, the appropriate population and life stages are addressed, appropriate dietary aspects are taken into consideration, and the appropriate exposure pathways are considered. For metals, frequency and duration of exposure, as well as exposure concentrations and metal species, are important parameters for the risk assessor to consider for accurate dose assessments.

4.2. HUMAN EXPOSURE ASSESSMENT

NAS/NRC (1994b) defines exposure assessment as "the determination of the intensity, frequency, and duration of actual or hypothetical exposures of humans to the agent in question. In general, concentrations of the substance can be estimated at various points from its source." Although there is no specific guidance exclusively for metal exposure assessment, EPA has published guidelines for exposure assessment (U.S. EPA, 1992c), exposure factors (U.S. EPA, 1997e, 1989a), exposure factors for children (U.S. EPA, 2002b), and assessment of early lifestage exposure (U.S. EPA, 2005). Additional reports and principles have been published by the Centers for Disease Control and Prevention (CDC, 2003) and IPCS (2000, 1999, 1994b).



Assessment of human exposures to metals, as with any chemical agent, includes:

(1) identifying how people come into contact with metals in the environment

(2) determining the concentrations of specific forms (speciation) of the metal in specific medial (e.g., soil, water, air, and biota)

(3) identifying the pertinent exposure metric (via consideration of dose-response assessment)

(4) estimating the exposure metric (e.g., oral intake, inhalation exposure concentration, blood concentration), which may involve quantifying relationships between exposure concentrations and intakes and

(5) identifying sources of uncertainty and natural variability and, where possible, quantifying these in estimates of exposure.

4.2.1. Background Levels

Metals are naturally occurring constituents in the environment. As a result of industrialization, current environmental levels of metals can be elevated relative to naturally occurring levels. This may result in a wide variability in the intake of some metals in food (e.g., seafood), drinking water, or air. Strategies for estimating metal concentrations in air, soil, and

Background Metal Concentration

As a result of industrialization, current environmental levels of metals can be elevated relative to naturally occurring levels. Depending on the purpose of the risk assessment, assessors should distinguish among naturally occurring levels, existing background levels, and contributions from specific activities at the local or regional level.

water are discussed in Section 3. In human health risk assessments, the term "background" refers to all existing metal sources except the targeted source. A particular challenge for the risk assessor may be assessing the metal levels associated with the source(s) of interest in light of levels derived from natural and other anthropogenic sources.

4.2.2. Bioavailability

The term "environmentally available fraction" refers to the portion of total metal in soil, sediment, water, or air that is available for physical, chemical, and biological modifying influences (Lanno, 2003) and represents the total pool of metal at a given time in a system that is potentially able to contact or enter an organism. Of that portion, the bioaccessible fraction (BF) is the amount that actually interacts at the organism's contact surface and is potentially available for absorption or adsorption (if bioactive upon contact) by the organism. Bioavailability is the extent to which bioaccessible metals (see Section 2.3) cross biological membranes, expressed as a fraction of the total amount of metal the organism is proximately exposed to (at the sorption surface) during a given time and under defined conditions.

The concept of metal bioavailability includes metal species that are bioaccessible and are absorbed or adsorbed (if bioactive upon contact) with the potential for distribution, metabolism, elimination, and bioaccumulation in the organism. Metal bioavailability is specific to the metal salt and particulate size, the receptor and its specific pathophysiological characteristics, the route of entry, duration and frequency of exposure, dose, and the exposure matrix. The metal salt is influenced by properties of the environment such as pH, particle size, moisture, redox potential, organic matter, cation exchange capacity, and acid volatile sulfides. Depending upon the assessment, it may be appropriate for the risk assessor to consider metal bioavailability and compare the bioavailable fractions used to estimate reference doses (RfDs), or the equivalent, to those measured in the diet, drinking water, or air.

Prediction of toxicity due to exposure to inorganic metals is complicated by wide variations in the bioaccessibility and bioavailability of accumulated metals. The form of the metal (chemical species, compound, matrix, and particle size) influences its bioaccessibility. In turn, the metal form is impacted by properties of the environment such as pH, particle size, moisture, redox potential, organic matter, cation exchange capacity, and acid volatile sulfides. Bioavailability (how much of the ingested metal interacts at the target site) is influenced by nutritional state (deficiency versus excess), age, sex, physiological state, pathological conditions, and interactions with other substances present.

Bioavailability/Hazard Relationship

If two substances were equally toxic at comparable levels of target organ exposure, the substance with the higher intrinsic bioavailability would pose the greatest risk.

It is important that the Exposure Analysis describes the same bioavailable fraction of the metal(s) of concern as that used when estimating the reference value (e.g., the RfD). For

example, measuring total metals in dietary items may include insoluble forms of the metal (particularly if soil contamination is present on the foodstuff), so effective exposure is overestimated. There are both direct and indirect approaches to address the relative bioavailability of metals in the environment: (1) conduct new animal toxicology studies using the metal form encountered in the site assessment; (2) use adjunct scientific data to derive an adjustment to the effective dose identified in the animal study (e.g., data on the distribution of chemical forms of the metal in the environment or at a contaminated site); or (3) use a default assumption that the metal in the environmental samples is the same as that tested. Of the three approaches, the first is more scientifically sound. The second option might be available in some circumstances but is usually precluded by time and financial resource limitations, and the third option, is the most health-conservative.

A fourth alternative conducted for site-specific assessments is for the risk assessor to estimate bioavailability through solubility studies or limited bioavailability studies of specific samples from the site. For example, arsenic bioavailability has been estimated for soils from various contaminated sites (Ng et al., 1998; Freeman et al., 1995, 1993) and also through a series of solubility studies of soil from a site contaminated with mine tailings (Ng et al., 1998; Salocks et al., 1996). Additional examples are animal feeding studies with juvenile swine for lead bioavailability adjustments or *in vitro* tests, although the Agency currently requires additional validation of the latter approaches before they can be used as the sole basis for making bioavailability adjustments (U.S. EPA, 2006a).

4.2.3. Susceptible Populations

Risk assessors must specifically consider population subgroups, which may have a greater risk to metals than the general population (U.S. EPA, 2006b). Factors influencing susceptibility to metals include life stage, life style, gender, reproductive status, nutritional state, pre-existing health conditions or disease, and genetic polymorphisms. Children and elderly people do not regulate metal uptake and distribution efficiently and may be at higher risk of accumulating toxic levels (U.S. EPA, 2006b). Pregnant and lactating women have a higher demand for essential elements, and lack of adequate levels of protein in the diet can affect the bioavailability of essential elements (NAS/NRC, 2000). Individuals with chronic liver or kidney disease may have a lower threshold for effects because these are two of the major target organs of metal toxicity. Several well-known, heritable genetic alterations affect people's ability to regulate Cu or Fe, resulting in various deficiency or toxicity problems (WHO/IPCS, 2002). Although many of these same factors are considered in all human health risk assessments, each has attributes specific to metals-associated risks.

4.2.3.1. *Life Stage*

In addition to higher intake per kilogram of body weight (Plunkett et al., 1992), children may also be more sensitive than adults to metal irritants since sensitivity to skin irritants is generally considered to decrease with age. Infants in the immediate postnatal period can also be more susceptible to systemic effects of metals because absorption of essential metals is poorly regulated (WHO, 1996). At the other extreme, older adults are more sensitive to metals that target the kidney (e.g., Cd) because renal function declines with age. Efficiency of intestinal uptake of some trace metals, particularly Zn and Cu, also declines as people age (WHO, 1996; IPCS, 1994).

4.2.3.2. *Demographics*

Differences in lifestyle influence metal exposure. The risk assessor should explicitly investigate different lifestyles of the population of concern. For example, the use of dietary supplements and other consumer products containing essential elements has increased. In addition, folk remedies such as colloidal silver "cure-alls" and folk remedies containing lead tetroxide may contain high levels of metals (McKinney, 1999; Yanez et al., 1994; Pontifex and Garg, 1985; Trotter, 1985; Bose et al., 1983; CDC, 1983, 1982, 1981; Geffner and Sandler, 1980). Smoking provides significant exposure to some metals (e.g., Cd) and can potentiate the effects of exposures from other sources, and excessive alcohol consumption can exacerbate metal effects.

4.2.3.3. *Pregnancy and Lactation*

Pregnancy and lactation increase demand for some essential metals, particularly Cu, Zn, and Fe (NAS/IOM, 2003; Picciano, 1996). Because of physiological changes that include higher Fe and Ca requirements, hormonal changes, and susceptibility to respiratory disease, Zuurbier and Van den Hazel (2005) suggested that pregnant women could be predisposed to the toxic effects of beryllium (Be), Pb, and Mn (2005). Recommended dietary allowances (RDAs) specific to pregnant and lactating women have been developed for a number of essential elements (NAS/NRC, 2000, 2001) and should be considered by risk assessors looking at these metals. Additionally, women lose significant amounts of Fe during menstruation, which may lead to increased absorption and toxicity of Cd (Berglund et al., 1994).

4.2.3.4. *Concurrent Damage or Disease*

In general, people with allergies and those with pre-existing medical conditions have higher-than-average biological sensitivity to *environmental stressors.* For example, diseases or treatments that damage the kidney or liver may increase sensitivity to metals that target these organs. Damage to the lung from smoking can potentiate effects of simultaneously or

subsequently inhaled metals, particularly those that act directly on the lung (e.g., Be, Cd, Cr, and Ni). Skin abrasions or other irritations also can alter exposures to and subsequent effects of metals (although dermal absorption is not a primary route of metals exposure for intact skin).

4.2.3.5. *Nutritional State*

Risk assessors should be aware that dietary differences can affect the absorption of metals, thus changing internal target dose. For example, lack of protein (or the type of protein) can decrease metal uptake, thus reducing potential risk. However, relatively little is known about this risk factor and nutritional state is an area for further study.

4.2.3.6. *Genetic Polymorphisms and Variability*

Risk assessors should be aware of several well-known, heritable, genetic polymorphisms that affect susceptibility to metals. The best known of these are two disorders that affect Cu metabolism: Wilson's disease and Menkes syndrome. Wilson's disease is an autosomal recessive abnormality (prevalence of 1 in 30,000) that causes impaired biliary excretion of Cu, resulting in accumulation in and damage to various tissues, particularly the liver, brain, kidney, and cornea; hemolytic anemia also can result. Menkes syndrome is an X-linked recessive disorder of Cu metabolism (prevalence of 1 in 200,000) that resembles Cu deficiency regardless of level of Cu intake (WHO/IPCS, 2002).

Hemochromatosis is another common inherited disorder. It is characterized by excessive Fe absorption, elevated plasma Fe concentration, and altered distribution of Fe stores (altered iron kinetics). One long-term effect is liver cirrhosis, with increased risk of liver cancer (NAS/IOM, 2003). Another Fe-related genetic polymorphism affecting Pb metabolizing enzymes is delta-aminolevulinic acid dehydratase (ALAD), which has been found to affect the relationship of bone Pb to the cumulative blood index, suggesting that the transfer of Pb from blood to bone is altered. It is suspected that genetic polymorphisms also exist for As metabolism (NAS/NRC, 2001), but these have not yet been defined.

Risk assessors should consider the possibility of genetic differences when assessing potential sensitization reactions. Chronic beryllium disease (CBD) is an immune response, with sensitivity determined by major histocompatibility (MHC) class II genes (U.S. EPA, 1998d). Similarly, sensitivity to Ni is related to the genotype of human leukocyte antigens (HLA)[3] (ATSDR, 2003).

[3] The major histocompatibility complex is a group of genes on chromosome 6 that code for the antigens that determine tissue and blood compatibility. In humans, histocompatibility antigens are called human leukocyte antigens because they were originally discovered in large numbers on lymphocytes. There are thousands of combinations of HLA antigens.

4.2.4. Environmental Release, Transport, and Fate

The exposure component of a human health risk assessment includes source characterization and analysis of fate and transport of the chemical of interest through environmental media. Models for transport and fate of metals from emission points to environmental receptors of importance to humans (e.g., soils, plants, or animals used in food and fiber) are covered elsewhere in this Framework document (see Section 3.2), as they are similar for both human health and ecological risk assessments. It is recommended the risk assessor conduct this portion of the assessment simultaneously for both human health and ecological assessments to ensure appropriate integration of the results. Human activities that affect the contact time of people with contaminated media also influence the route(s) and total amount of exposure.

4.2.5. Route-Specific Differences in Effects

Risk assessors should consider how route of exposure affects metal bioavailability and whether effects will occur at portal-of-entry or will be due to systemic, target-organ responses. Interactions among metals or other exogenous or endogenous compounds also can affect bioaccessibility of metals and are route dependent. Thus, many metal exposure issues are specific to the route of entry and will be discussed separately in the following sections.

4.2.5.1. *Inhalation Exposure*

Most airborne metals, with a few important exceptions (e.g., Hg and arsine) occur in particulate form. This necessitates certain considerations for inhalation exposure assessment, e.g., how particle size affects respirability (i.e., how much of the pollutant enters the respiratory system). Additionally, inhalation dosimetry for particles involves some distinctly different processes than for gases (i.e., deposition, clearance, dissolution, etc.), which are also influenced by particle size (U.S. EPA, 2004, 1997c). Particle size is thus an important factor in assessing metals exposure, with the focus generally being on particles less than or equal to 10 microns (Φ) in diameter (PM_{10}). Larger particles usually do not penetrate far into the respiratory tract and can be cleared to the ingestion route and swallowed. Larger particles may have a larger role as an irritant, affecting a person's eyes and nasal passages, and, if deposited in the uppermost reaches of the respiratory tract, may be transferred to the digestion tract. Thus, for exposure assessments involving measurements (e.g., using area or personal samples), the particle size is an important factor in determining inhalation exposure to metals.

Since inhalation is a primary route of exposure for metals, the risk assessor should have a good understanding of inhalation dosimetry methods and how inputs vary for metals. Key methods for inhalation dosimetry are described in EPA guidance documents (U.S. EPA, 2004, 1997c) and a number of models are available for calculating relative regional respiratory tract

deposition in rodents and humans (reviewed in U.S. EPA, 2004). The guidelines for reference concentration (RfC) development (U.S. EPA, 1990) cite the regional deposited dose ratio (RDDR) model, which has been used for development of a number of RfCs for metals. The multipathway particle dosimetry model (MPPD) developed by the Chemical Industry Institute for Toxicology (CIIT) and the Dutch National Institute of Public Health and the Environment (RIVM) was used in EPA's *Air Quality Criteria for Particulate Matter* (U.S. EPA, 2004). MPPD improves lung dose estimations by considering life-stage-specific parameters, particle clearance from the lung, and differences in oronasal breathing patterns with work load. The human equivalent concentration (HEC) is the concentration that is believed to result in the same dose to the respiratory tract region of interest as was received by the experimental animal species.

In developing inhalation exposure estimates, the risk assessor should pay careful attention to the form of the metal pertinent to the dose-response assessment (e.g., RfC, IUR). Simply measuring the total amount of a metal without regard to speciation may introduce uncertainties into inhalation exposure estimates or other exposure routes. Metal speciation affects a range of processes that change how the metal is deposited in the respiratory tract and subsequently distributed throughout the body and, consequently, its potential toxicity (Bailey and Roy, 1994; Oberdorster, 1992). For example, in assessing the risk of inhaled Cr, the assessor should consider speciation (e.g., Cr^{+3} vs. Cr^{+6}), as the dose-response assessment includes that specification. The bioavailability of metals via inhalation can be much higher than that of other intake routes. This may result in relatively high internal doses, even when intakes are similar to those from other routes. An example is the large contribution made by cigarette smoking to the body burden of Cd (e.g., Friis et al., 1998; Ellis et al., 1979). Variations in airway structure and respiratory conditions (e.g., as with age) may alter the deposition pattern of inhaled particles and contribute to variations in bioavailability (James, 1994; Xu and Yu, 1986; Phalen et al., 1985). For more information on the consideration of particle size in the dose-response assessment for RfCs and IURs, the risk assessor should refer to U.S. EPA, 1990. For metals having alternative Agency-developed dose-response metrics (e.g., blood Pb concentration), respirability, deposition, and clearance as well as absorption into the circulatory system may need to be addressed as part of the Exposure Assessment.

Risk assessors should be aware of emerging issues in inhalation dosimetry that may have important impacts on exposure assessments for metals (U.S. EPA, 2005). The developing literature suggests that current dosimetry models and traditional dose measures (such as concentration in mass/unit volume) may not adequately characterize human health risk to very small particles, such as particles $\leq$2.5 µm ($PM_{2.5}$) or <1 µm in diameter (nanoparticles). Much of the recent work on nanoparticle deposition has been conducted with metal oxide particles (e.g., titanium dioxide), and a growing body of literature is becoming available to the risk assessor. The bioavailability of Pb and other metals appears to increase with decreasing particle size,

particularly from the inhalation and oral routes of exposure, so risk assessors should be aware of the potential implications for bioavailability of metal nanoparticles.

Risk assessors should also consider exposure to metals in shower water, in which aerosolization can occur from the hot water tap. Though the magnitude of exposure from showering is unknown and comparable models do not exist for aerosolized metals (Wilkes, 1998), models have been developed to predict human inhalation exposures due to volatile organics from showering (e.g., Guo, 2002; Moya et al., 1999; McKone, 1987). Where appropriate, the risk assessor should address such inhalation exposures during the Risk Characterization phase.

4.2.5.2. *Dietary Exposure*

Dietary Exposure

Due to the diversity of the human diet, there may be wide variability in the intake of some metals in food (e.g., seafood), resulting in both temporal variability (e.g., spikes after a seafood meal) and geographic or cultural variability.

Risk assessors should be aware that dietary pathways represent a major exposure route for metals (Choudhury et al., 2001). Estimation of intakes of metals occurring in food requires information on the levels of metals in food and the amount of food consumed (NAS/IOM, 2003). A number of references provide assessors with national-scale information on dietary exposure to metals (Capar and Cunningham, 2000; Schoof et al., 1999a, b; Thomas et al., 1999; Bolger et al., 1996; Dabeka and McKenzie, 1995; Gunderson 1995; Tsuda et al., 1995; Dabeka et al., 1993). Although large-scale surveys of the metal contents of foods and food consumption patterns have been conducted (e.g., Egan et al., 2002; Ryan et al., 2001; U.S. FDA, 2001; O'Rourke et al., 1999; Thomas et al., 1999; U.S. DHHS, 1996), assessors should be aware that these surveys have several limitations for applications to human health risk assessment. Analysis is often conducted with "market basket" samples of packaged processed foods. With a few exceptions, such applications have not been empirically evaluated against biomarkers of exposure (Clayton et al., 2002, 1999; Choudhury et al., 2001). Risk assessors should be mindful that food consumption surveys are generally limited to short-term consumption (e.g., 1-3 days) and do not capture intra-individual variability that would affect long-term averages. Furthermore, dietary patterns may change over time (e.g., consumption of ethnic foods in childhood may change later), and, thus, patterns discerned at any given time may not accurately represent historical or future exposures. An additional challenge facing the risk assessor is integration of data from separate metal residue and food consumption surveys (e.g., Tomerlin et al., 1997). This leads to considerable uncertainty in estimates of metal exposure via the dietary route.

4.2.5.3. *Incidental Soil Exposure*

Infants and children can have enhanced exposures to metals through the pathway of surface dust because (1) they crawl and play in close proximity to surface dust and (2) they often mouth their hands (e.g., finger sucking) and objects in their environment. This causes an intake of surface dust that is generally greater than that which is normally found in adults (e.g., Barnes, 1990). On the other hand, infants have a large salivary response (i.e., they drool and spit up frequently), which may act to reduce overall dust intake. However, risk assessors should be aware that data are limited with regard to distinguishing between the quantity of dust ingested and the quantity of soil ingested. This parameter is important in connecting measured soil metal concentrations with surface dust ingestion that occurs in the indoor and outdoor environments (U.S. EPA, 1994a). Exposure assessment methods for direct soil ingestion are described in the Risk Assessment Guidance for Superfund (RAGS) (http://www.epa.gov/superfund/programs/risk/ragsa/index.htm). Additional guidance with respect to children (e.g., amount of soil a child may ingest) can be found in the *Child-Specific Exposure Factors Handbook* (U.S. EPA, 2002b). Few studies of soil ingestion in adults have been conducted; however, the estimates support the assumption that average daily soil ingestion rates of adults who do not participate in activities in which intensive exposure to surface dust and soil occur (e.g., occupational gardening, construction work) are lower than those of children (Calabrese et al., 1990; Hawley, 1985). Because concentrations of the metal contaminants in soil can be expected to vary with depth, risk assessors should consider soil metal concentrations at the depth appropriate to the metal(s) of concern as well as human behaviors and activities.

4.2.5.4. *Drinking Water Exposure*

Treatment of surface and/or ground water for human consumption removes dissolved organic carbon and suspended organic sediments that can form complexes with metals (AWWA, 1999). Thus, inorganic forms of metals in treated drinking water will often consist of the more bioavailable, water-soluble species. Treatment also removes bacteria that can participate in organification reactions of toxicological significance to humans (e.g., methylation of inorganic mercuric mercury).

Risk assessors estimating the intake of metals in drinking water will require information about concentrations of metals in the water and the amount of water consumed. Data on the metal content of tap water can be obtained from EPA's Office of Drinking Water. EPA's *Exposure Factors Handbook* contains exposure information on daily drinking water ingestion and incidental ingestion of water during swimming and showering (U.S. EPA, 1997e).

Generally, water metal concentrations are measured at the distribution point for municipal water delivery systems. Distribution systems within homes (pipes, storage containers, etc.) can contribute significant amounts of metals (e.g., Pb, Cu) to the home drinking water

(Graziano et al., 1996); consequently, the contribution of metals from home-based pipes, etc., is a source of uncertainty in the human health risk assessment.

4.2.5.5. *Dermal Exposure*

Metals absorption through the skin is limited because the dermal route of exposure is of less concern during a health risk assessment. However, some metals (e.g., Ni and Cr) have the potential to induce toxic and sensitization effects directly on the skin (U.S. EPA, 2001, 1992). Dermal exposure can also lead to intakes via other routes, such as oral exposure via hand-to-mouth transfer or ocular contact.

Potential sources of dermal uptake that the risk assessor should consider include small particles in contact with the skin; metal exposure during bathing, showering, and swimming (NAS/NRC, 2002); and the uptake of metals through damaged skin (e.g., irritated skin, sunburn). Dermal contact with metals in soil also represents a potential route of exposure, but the relatively low lipid solubility of most metals limits absorption through the skin (Paustenbach, 2000; Hostynek et al., 1998). Few studies have actually attempted to quantify the extent or kinetics of the dermal penetration of metals deposited on the skin, and the applicability of these studies to metal species and complexes that occur in surface dust or soil is highly uncertain.

4.2.6. Integrated Exposure

Approaches to integrating exposure across pathways and physiological routes of uptake include modeling, estimates of relative bioavailability, and the use of biomarkers.

4.2.6.1. *Modeling*

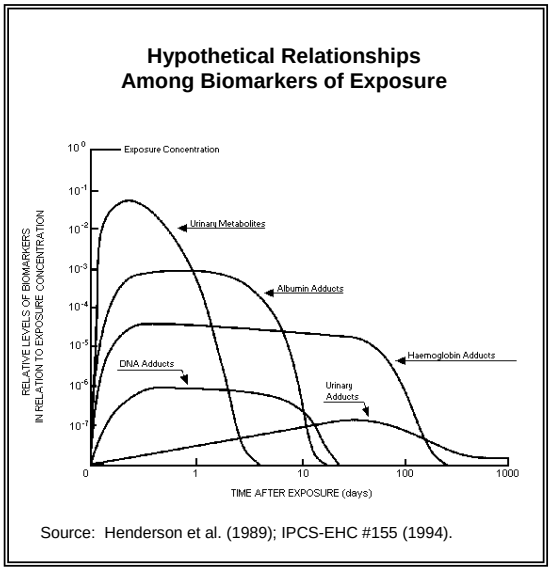
Risk assessors have access to only a few specific, integrated exposure models for metals. The Integrated Exposure Uptake Biokinetic (IEUBK) model for Pb in children (U.S. EPA, 1994a; White et al., 1998) was specifically developed for translating exposure measurements into risk estimates. The IEUBK model and background documentation are available on line at: http://www.epa.gov/superfund/lead/products.htm.

Risk assessors should not apply this model to other metals because it was derived using Pb-specific information and consequently is pertinent only to Pb. A multipathway exposure model specific for As has also been developed (Cohen et al., 1998). Less complex models linking adult exposures and blood Pb concentrations are available (Carlisle, 2000; Stern, 1996, 1994; U.S. EPA, 1996b; Bowers et al., 1994; Carlisle and Wade, 1992), and a stochastic human exposure model for Pb that is linked to a lead pharmacokinetics model may also be of use to the risk assessor (Beck et al., 2001; O'Flaherty, 1995).

Other models available to risk assessors are EPA's Total Risk Assessment Methodology (TRIM), which is being developed for multipathway risk assessment for air pollutants including

metals (http://www.epa.gov/ttn/fera/trim_gen.html); EPA's Stochastic Human Exposure and Dose Simulation (SHEDS) model, a probabilistic, physiologically based model that simulates aggregate human exposures and doses for various population cohorts of interest (Dang et al., 2003; Zartarian et al., 2000); EPA's Dietary Exposure Potential Model (DEPM) (Tomerline et al., 1997); RESRAD, a generic exposure model developed by the U.S. Department of Energy for risk assessment of radionuclides (U.S. DOE, 2001; LePoire et al., 2000); and 3MRA, a multimedia, multi-pathway, multi-receptor exposure model developed for screening-level risk-based assessment of chronic exposures to chemicals released from land-based hazardous waste management units (http://www.epa.gov/ceampubl/mmedia/3mra/).

4.2.7. Biomarkers



Source: Henderson et al. (1989); IPCS-EHC #155 (1994).

Risk assessors may find biomarkers of exposure, effect, and susceptibility useful as basic tools (IPCS, 2001, 1994). Centers for Disease Control (CDC) and the National Health and Nutrition Examination Survey (NHANES) are currently developing a national database to quantify and characterize body burdens (based on human blood and urine surveys) that includes Pb, Hg, Co, uranium (U), antimony (Sb), barium (Ba), Be, Cs Mo platinum (Pt), thallium (Tl), and tungsten (W) (CDC, 2005). Risk assessors can use this survey as a baseline measure against which the levels in receptor population individuals can be compared. The data are summarized in age, gender, and ethnicity categories. NAS also has completed a substantial amount of work in this area (NAS/NRC, 2006).

Integration of exposures across media, route, and time of exposure can be reflected in biomarkers of exposure. A biomarker of exposure is a measure of cumulative exposure to a metal and also of metal actually existing in the body, as occurs with chronic exposure to metals. However, such an approach may not be appropriate for metals that are not extensively bioaccumulated in tissues, and it does not differentiate between metal present in a tissue in a sequestered or inactive form and metal engaged in toxic or pathological processes. The approach also does not differentiate naturally occurring exposures from those due to added metals. For example, arsenobetaine is a nontoxic organic form of As found naturally in shrimp and other seafood. The analysis of total, unspeciated urinary As, without recognition of an individual's dietary history, could lead to an overestimation of exposure if the risk assessor does not account for seafood consumption (NAS/NRC, 1999). Thus, use of biomarkers increases the need for comprehensive, multipathway assessments of exposure. When available, reference or baseline levels of biomarkers of exposure should be incorporated into the assessment.

4.3. HAZARD CHARACTERIZATION

Hazard identification (or hazard characterization) is "the determination of whether exposure to an agent can cause an increased incidence of an adverse health effect, such as cancer or birth defects, and characterization of the nature and strength of the evidence of causation" (NAS/NRC, 1994b). This includes identification of the target organ(s), consideration of any route-specific issues, evaluation of the adversity of the effects observed, and consideration of relevance to humans. Key points and metals-specific concepts to be considered in hazard characterization are detailed in the following sections.

4.3.1. Mixtures and Interactions

In most settings, individual metals exist as components of mixtures with other metals and/or organic substances (ATSDR, 2004; NRC, 1988). Effects of the metals in mixtures may be synergistic, additive, subadditive, potentiating, and/or antagonistic. Interactions among metals occur by competition for binding locations on specific enzymes or on cellular receptors during the processes of absorption, excretion, or sequestration at the target site. The presence, amounts, and interactions of all inorganic metals are important when considering and evaluating the effects of exposure and resulting human health risk assessment.

Metals usually exist as components of mixtures with other metals and/or organic substances (ATSDR, 2004; NRC, 1988). Because the information or guidance on risks of metal mixtures is limited, risk assessors should follow published guidance for the human health risk assessment of chemical mixtures in general (U.S. EPA, 2000b, 1986) and cumulative risk guidance (U.S. EPA, 2003e).

Only a few controlled studies exist on the interactions of metals relevant to levels found in the environment (see ATSDR, 2004, on mixtures of (1)As, Cd, Cr, and Pb; and (2)Cu, Pb, Mn, and Zn). Risk assessors may use the current default approach, which assumes additivity of the doses for each metal as it will produce estimates that are overly-cautious. This approach, which involves calculation of a hazard index (HI), is most appropriate for chemicals that produce the same effects by similar modes of action (MOAs). However, differing potencies of metals with similar MOAs should be accounted for by converting chemical concentrations into an equitoxic dose using either toxic units (TUs) or toxicity equivalence factors (TEFs). In the case of chemicals with different MOAs, the risk assessor should consider estimating separate effect-specific HIs for each chemical in the mixture

Metal-Binding Proteins

Metallothioneins (Ag, Hg, Cu, Bi, Cd, Pb, Zn) **t**
Transferrin (Fe, Al, Mn) **t**
Ferritin (Fe, Cd, Zn, Al, Be) **s**
Ceruloplasmin (Cu, Fe) **tr**
Lead-binding protein(s) (Pb) **s**
Membrane carrier proteins **t**

s = storage; **t** = transport; **tr** = transform

using the RfD as the toxicity value for each effect. Newer EPA guidance provides a number of quantitative approaches for characterizing mixture risks (described in detail in U.S. EPA, 2000b, 1986).

The terms *molecular mimicry* and *ionic mimicry* have been applied to situations in which a metal forms a complex with an endogenous ligand and the resulting compound mimics the behavior of a normal substrate, disrupting normal function (Ballatori, 2002; Clarkson, 1993). Molecular or ionic mimicry may be viewed as a form of metal-metal interaction. Most examples involve the replacement of an essential metal with a nonessential metal. For example, Cd can mimic and substitute for Zn and Ca. Additionally, many different proteins in the body complex with metals which may modify their toxicity and kinetics (e.g., some metals bind with albumin for purposes of transport in the circulatory system and across cell membranes or within cells). Some proteins have different binding kinetics for the various metals, resulting in specific protein-metal interactions. Risk assessors should be familiar with these metal-binding proteins to correctly interpret the bioavailability of individual metals within a mixture and the potential use of protein expression as a biomarker of metal exposures.

Many of the interactions between essential metals are related to maintaining optimal nutritional levels by synergisms and antagonisms at both physiological and extrinsic (dietary) sites. World Health Organization (WHO) publications (IPCS, 2002; WHO, 1996) have summarized these homeostatic interactions, which are often complex (e.g., excess Ca in the diet may induce signs of Zn deficiency, even if the Zn intake is normal). Similarly, excess Zn in the diet may aggravate Fe deficiency.

Interactions between essential and nonessential metals are very common (e.g., Cd uptake can mimic that of Zn). Similarly, among anions, mimicry of the sulfate and phosphate ions occurs. However, the risk assessor should be aware that validated data in humans are rare, and that applications of this phenomenon are best limited to screening-level assessments. Two nonessential metals may compete for passive transport across common sites on a membrane or with an essential metal on an active binding site. These effects may not be additive and likely relate to relative binding strength. One metal may affect one site and another metal may affect a different site; this can include both active and passive transport or binding sites and may or may not include interactions with essential metals. These effects often will be additive. The risk assessor should be familiar with the MOAs of each metal of concern to develop at least a general understanding of whether the mixture effect is likely to be additive or more than additive.

Metals can be active at most cellular sites where organic toxicants have their effects and directly interfere with receptor activation (Stoica et al., 2000), ion channel regulation (Kiss and Osipenko, 1994), cell signaling (DeMoor and Koropatnick, 2000), cell adhesion (Prozialeck et al., 2002), and gene transcription (Meplan et al., 2000). Thus, metals are not readily distinguished from organic substances in the range of their potential mechanisms of action at the cellular and molecular level, so the risk assessor can transfer knowledge about toxicity across

chemicals. Additionally, co-occurrence of metals with organic substances can change the bioavailability and increase or decrease absorption. For example, in the diet, citrates and histidine are known to enhance Zn absorption, whereas ascorbate can modify Fe-Cu antagonisms. Low protein content may increase the absorption of Cd and Pb, and oral contraceptives may influence the metabolism of Fe, Cu, and Zn. The risk assessor should be aware of these conditions to avoid over- and underestimating risk.

4.3.2. Essentiality

Essentiality

Essentiality should be viewed as part of the overall dose-response relationship. The shape of this relationship can vary among organisms. For a given subpopulation, reference doses designed to protect from toxicity of excess should not be set below doses identified as essential for that subpopulation.

Certain elements are nutritionally essential to humans and play a key role in physiological or biochemical processes (NAS/IOM, 2003; IPCS, 2002; WHO, 1996). Elements essential to other organisms may not be essential to humans and vice versa. Adverse nutritional effects can occur if essential metals are not available in sufficient amounts, and nutritional deficits also can be adverse and increase the vulnerability of humans to other stressors, including those associated with other metals. Essentiality should be viewed as part of the overall dose-response relationship, and *reference doses* designed to protect from toxicity of excess should not be set below doses identified as essential.

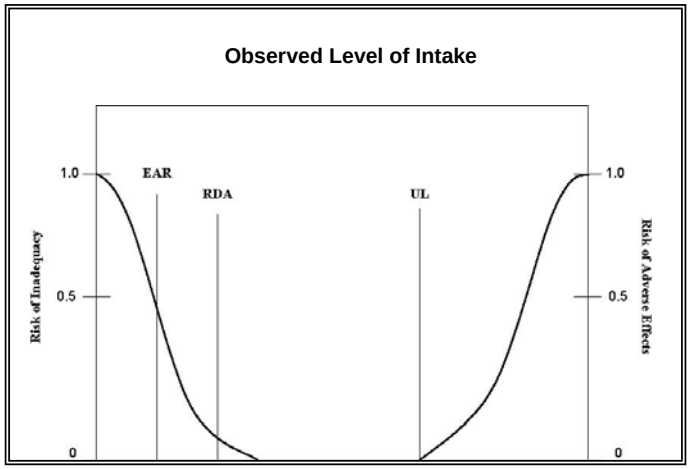
Metals that are currently deemed nutritionally essential for humans are Co, Cr III, Cu, Fe, Mg, Mn, Mo, Se and Zn (Table 4-1). Some metals (e.g., B, Ni, Si, V, and perhaps As), while not essential to human health, may have some beneficial effects at low levels of exposure (NAS/IOM, 2003). Risk assessors should consider the essential elements as comprising three groups: those that are cations (Zn, Fe, Cu, Mn, Cr), those that are anions (Mo, Se), and those that are a bio-inorganic complex (i.e., the Co complex, cobalamin). The homeostatic mechanisms differ for each group, and risk assessors can use this knowledge to generally classify the types of health effects that might occur and the potential bioavailability of the metal. In general, the gastrointestinal tract and the liver regulate the uptake and transfer of cations (e.g., Fe, Zn, Cu). The anionic group is more water-soluble and is less reactive with N, S, P, O, and hydroxide groups than are cations. They are absorbed very efficiently through the intestine and their subsequent compartmentalization and excretion is by manipulation of their oxidation and methylation states; total body burden is regulated by renal excretion. The risk assessor should be aware that homeostatic controls do not typically apply to effects at the portal of entry, so effects can be seen at lower doses than those required for systemic responses.

The risk assessor should view *essentiality* as part of the overall dose-response relationship. The risk assessor should use the entire dose-response relationship, from very low (inadequate) doses to high (toxic) doses (see text box) when determining an acceptable upper

Table 4-1. Metal essentiality for humans

Nutritionally essential metals	Nutritionally nonessential metals	
Cobalt II, III	Aluminum III	Nickel II
Chromium III	Antimony III, V	Niobium* V
Copper 0, I, II	Arsenic III, V	Palladium* 0, II
Iron II, III	Barium II	Platinum* 0, II, IV
Magnesium II	Beryllium II	Rubidium I
Manganese II, IV	Bismuth III, V	Silicon* IV
Molybdenum IV, VI	Boron III	Silver 0, I, II
Selenium II, IV, VI	Cadmium II	Strontium II
Zinc II	Cesium* I	Tellurium* II, IV, VI
	Chromium VI	Thallium I, III
	Gallium* III	Tin II, IV
	Germanium* IV	Titanium IV
	Gold 0, I, III	Tungsten VI
	Indium* III	Uranium IV, VI
	Lead II, IV	Vanadium III, V
	Lithium I	Zirconium* IV
	Mercury 0, I, II	

* Limited human data for these metals.



exposure limit. Several agencies have developed guidance for selecting a benchmark dose that is not too low (and, therefore, likely to result in deficiency) or too high (and likely to result in toxicity to some segment of the population). IPCS (2002) guidance describes the use of an "Acceptable Range of Oral Intake" (AROI), which estimates the minimal requirement to prevent deficiency and an upper limit that will produce toxicity. The NAS Food and Nutrition Board (FNB) in conjunction with the Institute of Medicine (IOM, 2001; NAS/IOM, 2000) developed the Dietary Reference Intakes (DRIs) program and reformulated RDAs (now known as RDIs) using the estimated average requirement (EAR) or adequate intakes (AIs). They also developed a tolerable upper intake level (UL), which is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. The UL is based on a risk assessment model similar to that used by EPA to set the RfDs and is intended to protect the population from adverse health effects resulting from excess exposure to a compound. ULs are available for all the essential metals and for B, Ni, and V. ULs do not take into account sensitive

or immuno-compromised populations. ULs may differ from RfDs because they are derived from human studies rather than animal studies and use smaller uncertainty factors. Additionally, the risk assessor should be cautioned that RfDs are intended to cover sensitive subpopulations, whereas RDAs are estimated to satisfy the nutritional needs of 97.5% of the healthy U.S. population. RDAs are specific to different age groups and genders, with listings for 16 different age-sex and six age-pregnancy combinations (NAS/IOM, 2003).

4.3.3. Forms of Metals

Unlike organic chemicals, metals are neither created nor destroyed by biological or chemical processes. However, these processes can transform metals from one valence state to another and can convert them between inorganic and organic forms. Information developed for one form of a metal may not be directly applicable to other forms. Different valence states (species) of the same metal affect bioaccessibility and bioavailability, and they elicit different responses in the human body. The particle size and environmental matrix (water, soil, air), within which the metal is embedded, influence exposure amount, rate, and route, particularly for the inhalation pathway, which can then result in different target organs and response levels. Therefore, the risk assessor should consider which form of the metal of interest is being assessed. If exposure or effects information has been developed for a different metal species, the risk assessor should either make appropriate adjustments or acknowledge this as a significant uncertainty in the Risk Characterization. For example, Cr(III) is essential in the diet, whereas inhaled Cr(VI) is carcinogenic.

Risk assessors should be aware that information developed on the health effects of one form of a metal may not be directly applicable to other forms, particularly organometallics; other guidance documents should be consulted when conducting risk assessments for organometallics.

4.3.4. Toxicokinetics/Toxicodynamics

Toxicokinetics

Toxicokinetics describes the series of processes that dictate the disposition of a substance in or on the body after exposure occurs and processes related to deposition on the body surfaces (also considered in exposure assessments), absorption, distribution, metabolism, and excretion (ADME).

Homeostatic mechanisms such as binding of metals to proteins can introduce significant complexities to hazard assessments for metals, with significant quantitative effects once these mechanisms are overwhelmed. Certain metal compounds bioaccumulate in human tissues, and it is important to recognize that such bioaccumulation is related to toxicity (SAB, 2006; see Section 2.3.1 for a definition and more detailed discussion of bioaccumulation). Since not all tissues may be of "interest" from a human health perspective, net accumulation in human tissues may or may not be relevant in the hazard characterization of metals (see, for example, Section 4.3.4.2 for a

discussion of metal sequestration and subsequent remobilization). Further, there are no available simple metrics that allow quantification of the potential for human bioaccumulation of metals, although a full pharmocokinetic model can be used to estimate metals bioaccumulation and distribution in human tissues. Additional discussion of the potential for remobilization of sequestered metals is in section 4.3.4.2. All these processes can be described through the use of physiologically based pharmacokinetic (PBPK) models. Integrated descriptions provide metrics of internal dose (including biological markers of exposure) that can be used by risk assessors to improve the quantitative basis of dose-response assessments. Unique features of metals that result in differences in toxicokinetic behavior of metals as compared to organic substances are shown in Table 4-2.

Bioaccumulation of metals is the net accumulation of a metal in the tissue of interest or the whole organism that results from *all environmental exposure media*, including air, water, solid phases (i.e., soil, sediment), and diet, and that represents a net mass balance between uptake and elimination of the metal (SAB, 2006).

Table 4-2. Summary of major differences in kinetic behavior of organic compounds compared to metals and inorganic metal compounds in humans

Organics	Metals
Tissue uptake is most commonly a blood flow-limited process, with linear portioning into tissues.	Metals and their complexes are often ionized, with *tissue uptake* (membrane transport) having greater potential to be diffusion-limited or to use specialized transport processes.
Metabolism is generally extensive and often species-specific.	*Metabolism* is usually limited to oxidation state transitions and alkylation/dealkylation reactions.
Persistence in body fat is common because of lipid solubility (not capacity-limited).	Often *sequestered*, bound to specific plasma or tissue proteins (intrinsically capacity-limited) or bone.
Due to complex metabolism, organics may be *eliminated* by excretion in urine after biotransformation from lipophilic forms to hydrophilic forms, in bile after conjugation to large organic molecules, or in exhaled air if not metabolized.	Predominantly *eliminated* in urine because metal compounds are generally small molecules and are hydrophilic. As a result of protein binding, may be excreted via hair and fingernails.
Generally substance-specific *homeostatic mechanisms* are not available.	Essential metals have *homeostatic mechanisms* that maintain optimum tissue levels over a range of exposures.
Interactions with other structurally similar compounds may occur, especially during metabolism.	*Interactions* among metals and between metals and organics are numerous and occur commonly during the processes of absorption, excretion, and sequestration.

Source: Adapted from Golub et al. (2004).

4.3.4.1. *Absorption*

Absorption is a process by which an administered substance enters the body. *Bioavailability* is a term often used to describe the degree of absorption. Two elements of the absorption process are critical for evaluating systemic doses of metal compounds, both the degree and rate of absorption. Although information on both of these parameters is ideal for developing a quantitative estimation of systemic doses, information on the degree of absorption is more commonly available for most chemicals. Metals have a number of unique properties that impact their absorption across biological membranes. Key factors affecting the absorption of metals include solubility, particle size, valence state, lipophilicity, and the exposure matrix. Soluble forms of the metal are more readily absorbed since the metal ion itself is typically the absorbed entity. The bioavailability of metals increases as particle size decreases. However, in the lung particle size also determines the site of deposition and thus the clearance mechanisms that can ultimately result in systemic uptake (via transport to the lymph system following macrophage engulfment) or the GI tract (via mucociliary transport). Chemical speciation in terms of valence state can affect absorption. Recent progress in identifying metal transporters suggests that generalizations are not appropriate, and each metal should be assessed in terms of its ability to access transporters and the presence of transporters in potential target organs. In general, lipophilic compounds will be absorbed more readily than hydrophilic ones. For example, human skin is not very permeable, and it provides a good barrier against dermal absorption of metals and metal compounds; elemental Hg and dimethyl Hg are notable exceptions. Risk assessors should note the complexities in absorption processes since they have direct implications on metals risk assessment, primarily in requiring detailed consideration in extrapolating across different exposure conditions or animal species. Absorption can vary dramatically for different forms of the same metal, for the same form of metal in different matrices, among different species, and across different routes of exposure. Therefore, it is not appropriate to assume concordance in absorption of metal compounds without a detailed evaluation (and documentation) of the scientific basis for such an assumption. For example, empirical information on dermal absorption of metals should be consulted when available (Stauber et al., 1994; Wester et al., 1992; Hursh et al., 1989; Ilyin et al., 1975), and similar considerations apply to other routes of exposure.

4.3.4.2. *Distribution*

The unique features of metals influence their distribution to potential target organs and the subsequent target tissue doses. The distribution of metals reflects their transport and accumulation in the body within tissues, blood or plasma, or other extracellular space. Partitioning to blood and cellular components, particularly via interactions with proteins, is of particular importance for metal risk assessment. Retention in tissues of metals or metal

compounds generally is related to formation of inorganic complexes or metal protein complexes (e.g., Pb in the bone compartment and Cd in tissues bound to low-molecular-weight metallothionein proteins). Risk assessors should be aware that retention of metals in the body by protein binding or sequestration in a nontoxic form allows the metal to reside in the body without producing a toxic or pathological effect. For example, As and Hg have relatively short biological half-lives that can be measured in days, whereas Cd and Pb can be bound or sequestered in inactive forms for years. Cd is retained in soft tissues (e.g., liver and kidney) for 10 to 20 years by intracellular binding with metallothionein. Metal binding to proteins is capacity-limited, and toxicity to target organs occurs when the binding capacity is exceeded. Thus, the potential for toxicity exists in older adults for metals with long half lives that are initially adequately sequestered. Conversely, retention in tissues is a dynamic equilibrium and can be a source of internal exposure long after the external exposure source has been removed. For example, Pb in bone can be mobilized during pregnancy and lactation or as a result of osteoporosis (USEPA IRIS, http://www.epa.gov/iris/subst/0277.htm). The risk assessor should consider all the aspects of metal distribution in the body (i.e., binding and sequestration plus release processes) when estimating likely target dose. The risk assessor should also note the uncertainty associated with lack of information to complete a quantitative analysis of these processes during the Risk Characterization.

4.3.4.3. *Metabolism*

Metabolism of metals is limited to oxidation-reduction reactions or alkylation/ dealkylation reactions. In these reactions, new inorganic species or metal organic complexes may be formed, but the metal ion persists. Nevertheless, differences in these transformation pathways among human populations or across species have practical implications for risk assessment because different species of the same metals often have very different toxicities. Because of this, the risk assessor should fully explore available data on metal metabolism. For example, As can be metabolized to organic forms that are less toxic than the inorganic As to which an individual is initially exposed.

4.3.4.4. *Excretion*

Risk assessors should be aware of the number of qualitative differences in metal excretion as compared to organic compounds. These include the greater likelihood for excretion in urine and the propensity for metals to be excreted via hair and nails. In addition to reducing the target dose, risk assessors can use these excretion routes to develop biological markers of exposure for many metals.

Although metals share many similar characteristics, their excretion kinetics can vary dramatically, primarily because of differences regarding sequestration in bone or binding to

specific proteins. This reduces the rate of excretion (or generates a biphasic excretion curve with two or more distinct excretion half-lives). Risk assessors should assess each metal individually to incorporate excretion rates in the calculations of target dose and subsequent hazard assessment.

4.3.4.5. *Kinetic Modeling*

Physiologically based pharmacokinetic/pharmacodynamic (PBPK/PBPD) modeling of metals entails the mathematical description and modeling of their absorption, distribution, metabolism, and excretion (ADME). A typical PBPK model consists of multiple compartments representing tissues or tissue groups that are linked by blood flow. PBPD models describe the relationship between target tissue dose and health endpoints or target tissue effects. Combined use of PBPK and PBPD models provides understanding of the complex relationships between exposure and target organ effects. Risk assessors may find that these models are valuable risk assessment tools for purposes of interspecies, high-dose/low-dose, route-to-route, and exposure scenario extrapolations (Krishnan and Andersen, 1994). A PBPK model allows the risk assessor to define the relationship between external exposure and an internal measure of a biologically effective or toxic dose in both experimental animals and humans, thus increasing the precision of extrapolating effects thresholds to humans. Use of PBPK models can account for nonlinear uptake, metabolism, and clearance; toxicity associated with products of metabolism rather than the parent chemical only; and tissue interactions. The underlying assumption of PBPK is tissue dose equivalence, i.e., that health effects are caused by the toxic form(s) of the chemical measured at the biological target (Krishnan and Andersen, 1994).

PBPK models historically have been developed and used for risk assessment mainly with volatile organic compounds (VOCs) (e.g., methylene chloride) (Andersen et al., 1987), but PBPK models have recently been applied to some metals (White et al., 1998; Clarke, 1995). There are currently three main Pb risk assessment PBPK models. *The O'Flaherty model* (O'Flaherty, 1995) is a PBPK model for children and adults. It includes the movement of Pb from exposure media (i.e., intake via ingestion or inhalation) to the lungs and gastrointestinal tract and subsequent exchanges between blood plasma, liver, kidneys, and richly and poorly perfused tissues; and excretion from liver and/or kidney. *The Leggett model* (Leggett, 1993) allows risk assessors to simulate lifetime exposures and can be used to predict blood Pb concentrations in both children and adults. The EPA has performed a comparison of these adult Pb risk assessment models (http://www.epa.gov/superfund/lead/products/adultrevie

Metal Toxicity

The organ or tissue in which metal toxicity occurs may differ from the organ or tissue(s) in which the metal accumulates and may be affected by the metal's kinetics. Effects at the portal of entry do not depend on bioavailability. Both the exposure route and the form of the metal can affect a metal's carcinogenic potential and its noncancer effects.

w.pdf) . EPA developed the Integrated Exposure Uptake Biokinetic (IEUBK) model to predict Pb levels in children (U.S. EPA, 1994a) and recommends that it be used as the primary tool for Pb risk assessment at Superfund and RCRA corrective action sites (OSWER Directive, 1998; http://www.epa.gov/superfund/lead/products/oswer98.pdf).

Risk assessors can review differences in kinetic behavior between metals and VOCs in O'Flaherty (1998). In brief, these include: (1) oral bioavailability, (2) inhalation bioavailability, (3) cellular uptake, (4) nutritionally essential and nonessential metal interactions, (5) protein-binding behavior and function, (6) incorporation into bone or hair, (7) metabolism, and (8) excretion. Moreover, risk assessors should keep in mind that many of the processes controlling the disposition of metals are intrinsically capacity-limited and can result in extended residence times. Risk assessors should use multiple lines of evidence to understand the kinetics and, therefore, the hazard of metal sequestration and elimination. The major challenge faced by the risk assessor when using PBTK models for metals is to balance the complexity of the biology with the data available to parameterize the model. Estimation of many parameters from the same data or insufficient data (over-parameterization) leads to greater uncertainty in model predictions and limits the utility of the model for regulatory purposes.

4.3.5. Metal Toxicity

Diversity in observed toxicities of different metals likely reflects the variety of biochemical mechanisms by which they exert their effects and variability in their toxicokinetic properties. At least five metals are known carcinogens, and several other effects of metals are also well documented, including effects on the neurological, cardiovascular, hematological, gastrointestinal, musculoskeletal, immunological, and epidermal systems.

4.3.5.1. *Noncancer Effects of Metals*

Metals and metal compounds have very diverse toxicological profiles. For risk assessment purposes, selected critical effects serve as the basis for deriving threshold or benchmark toxicity values (e.g., RfDs) and are defined as "the first adverse effect, or its known precursor that occurs to the most sensitive species as the dose rate of an agent increases" (U.S. EPA, 2005). Both the mechanism of toxicity and the critical effect may vary with the form of the metal. Additionally, short-term exposures may produce target organ effects very different from those produced by a similar dose over a longer period of time. Short-term, high-level exposure by ingestion may give rise to well-recognized acute toxicity syndromes, usually involving the gastrointestinal tract initially and possibly, secondarily involving the renal, cardiovascular, nervous, or hematopoetic systems. Survivors of acute high-dose As ingestion usually experience multiple organ effects, sometimes with long-term sequelae. Long-term, low-dose exposures from ingestion of metals in food and water generally cause an accumulation in

target organs over time. Such exposures can involve any organ system but do not usually produce overt gastrointestinal symptoms. For example, low-level, long-term exposure to Cd in food—sometimes combined with inhalation exposure from cigarette smoking—will cause Cd to accumulate in target organs (e.g., kidney) but will not produce any obvious clinical effects until "excess" capacity is diminished to a point where the normal function is lost (e.g., onset of renal disease and/or osteoporosis later in life).

In addition to considering systemic effects, the risk assessor should also examine portal-of-entry effects. Unlike systemic effects, which may be route-independent, portal-of-entry effects are not observed following other routes of exposure. For example, dermal irritation, sensitization, and allergic responses from metals can occur without absorption and systemic responses.

4.3.5.2. *Carcinogenic Effects of Metals*

At least five transition metals—As, Cd, Cr(VI), Be, and Nil—are accepted as human carcinogens in one form or another or in particular routes of exposure (IARC, 2004b; NTP, 2002) and inorganic Pb compounds are considered probable human carcinogens by EPA's IRIS program, while IARC (2004a) has concluded that there is limited evidence of carcinogenicity to humans (see: http://www.epa.gov/iris/subst/0277.htm#carc and http://monographs.iarc.fr/htdocs/announcements/vol87.htm). Other metals have mixed evidence regarding potential carcinogenicity. Therefore, risk assessors should pay careful attention to approaches for cancer risk assessment as applied to metals. Several guidance documents are available for use by the risk assessor in developing or interpreting cancer risk assessments (e.g., U.S. EPA, 2005), as are international efforts that provide guidance on assessing human relevance of tumors identified in animals (Cohen et al., 2004).

Nickel and Pb compounds and Cr and Cr compounds are well-established contact allergens. Other metals that have been cited as contact allergens include Cu (WHO/IPCS, 1998), Co salts (AIHA, 2003), organomercurials (AIHA, 2003), Be (IPCS, 1990b), palladium (Pd) (Kimber and Basketter, 1996), and gold (Au) (Kimber and Basketter, 1996). Although there is some connection between skin and respiratory sensitization, it does not follow exact rules, and the dermal mode is a much more common reaction to metals.

A key consideration for the risk assessor in cancer risk assessment is the determination of the MOA of carcinogenesis, a general description of how the chemical causes cancer. The MOA determines human relevance of observed animal tumors, any route-specific differences (e.g., carcinogenic at the portal of entry via the inhalation route, but not carcinogenic via the oral route), and the approach used for extrapolation from experimental doses in animals to environmentally relevant human doses. In particular, the MOA evaluation is a key consideration in whether a linear or nonlinear approach is used to extrapolate to low doses. The MOA is

known for some, but not all, metals. For those for which the MOA is unknown, the risk assessor should refer to the Cancer Guidelines (U.S. EPA, 2005) for guidance.

4.3.5.3. *Issues Related to Evaluation of Toxicity Tests for Metals*

As with any hazard assessment, risk assessors prefer a robust dataset on toxic responses of the metal(s) of concern for key endpoints (e.g., irritation and sensitization, systemic noncancer toxicity, and genotoxicity or tumorigenicity). In many cases, metals will be well-studied, and thus, human studies (epidemiology, controlled clinical studies, or case reports) will be available to aid in hazard characterization. For metal compounds for which adequate human data are not available, the risk assessor must rely on animal toxicity studies. U.S. EPA has established guidelines for assessing the adequacy of a database for derivation of chronic human health risk values such as RfDs and RfCs (U.S. EPA, 2002a) and has provided guidance for evaluating the "weight of evidence" for carcinogenicity (U.S. EPA, 2005). These generic guidelines are applicable to metals as well as organic compounds as long as the risk assessor considers the following metal-unique aspects of hazard determination:

- **Adequate controls.** When a salt of a metal is administered to the test animals, the risk assessor should evaluate that a suitable control group was used, specifically that any potential for salt-induced toxic responses is appropriately assigned probable cause.

- **Dosing solubility, ionization, hydration, and speciation of metals administered in water.** Metal compounds may be in suspension or in solution and may be differentially hydrated depending on the concentration in which they are prepared and the length of time the preparation stands, potentially resulting in different pharmacokinetic and toxic properties. Water pH and mineral content also are relevant factors to be considered by the risk assessor.

- **Trace element content of food and drinking water.** Because of the well-known interaction of metals with essential trace elements, the trace element content of animal feed and drinking water or of vehicles used for gavage or injection studies should be reported or controlled. Inconsistent results across experiments could be due to this factor.

- **Acute stress in the experiment**. A component of acute stress in the experiment can induce hepatic metal-binding proteins (acute phase proteins) and alter the toxicity of a given administered dose.

To achieve an adequate internal dose for the study of toxicity, animal toxicologists often use bioavailable forms of metals. For the initial characterization of a toxicity syndrome, it is not practical to simultaneously test all forms of a metal that may be involved in human exposures. For example, Al researchers commonly use aluminum lactate, which is known to reliably provide elevated tissue concentrations in laboratory animals, or aluminum maltolate, which

provides a stable ion pool in water solution. However, a risk assessor is very unlikely to conduct an assessment of Al in its lactate or maltolate form. Thus, the risk assessor should be aware that failure to adjust the toxicity data generated from water-soluble metal species to the appropriate, less soluble species of concern introduces uncertainty. There are both direct and indirect approaches to address the relative bioavailability of metals in the environment: (1) conduct new animal toxicology studies using the metal form encountered in the site assessment; (2) use adjunct scientific data to derive an adjustment to the effective dose identified in the animal study (e.g., data on the distribution of chemical forms of the metal in the environment or at a contaminated site); or (3) use a default assumption that the metal in the environmental samples is the same as that tested. The first approach is more scientifically sound but often is precluded by time and financial resource limitations; the third option generally is the most health-conservative.

A fourth alternative to conducting site-specific assessments is for the risk assessor to estimate bioavailability through solubility studies or limited bioavailability studies of specific samples from the site. For example, arsenic bioavailability has been estimated for soils from various contaminated sites (Ng et al., 1998; Freeman et al., 1995, 1993) and also through a series of solubility studies of soil from a site contaminated with mine tailings (Ng et al., 1998; Salocks et al., 1996).

4.3.6. Dose-Response Assessment

The result of the hazard characterization is a determination of the key noncancer and cancer endpoints related to exposure to the metal of interest. The risk assessor then uses these data as the input to the dose-response assessment to "characterize the relationship between exposure or dose and the incidence and severity of the adverse health effect" (NAS/NRC, 1994b). Assessors should consider the factors that influence dose-response relationships, such as intensity and pattern of exposure, age, and lifestyle variables. Traditionally, separate approaches have been used for dose-response assessment for noncancer and cancer endpoints. For noncancer endpoints, the result of the dose-response assessment is an RfD for oral or dermal exposure or an RfC for inhalation exposure. For cancer assessment, the approach depends on the chemical's MOA. Classically, the result of the cancer assessment is a measurement of the risk per unit dose, either as a slope factor or unit risk.

A key consideration for the risk assessor when deriving metal dose responses is to express the exposure potential and the toxic response as the same metal species. In general, for systemic effects of soluble metal salts, the risk assessor should express toxicity in terms of the dose of the metal ion rather than the metal salt. In contrast, if the toxicity is related to a specific compound, particularly for portal-of-entry effects, risk assessors should express it in terms of the compound, rather than the ion. These differences should be considered when applying toxicity values in risk assessments. For example, in IRIS, Se is listed as "selenium and compounds," and there are separate assessments for "nickel, soluble salts," "nickel subsulfide," "nickel refinery

dust" (a mixture), and "nickel carbonyl" (a highly reactive compound that behaves differently from other nickel compounds). In some situations, the toxicity of the anion needs to be considered. For example, there are separate IRIS documents for Ag and silver cyanide. However, careful consideration of the chemical form has not been applied historically to all such documents, and the risk assessor should carefully consider the applicability of the chosen toxicity values to the chemical forms of interest, paying close attention to solubility, bioavailability, and physical/chemical properties as well as available toxicity data.

Considerations in Risk Characterization

Variability. Inter-individual biological differences exist within an animal or human population, or measurement differences exist owing to method imprecision.

Uncertainty. Data are unavailable.

Incertitude. Knowledge about key relationships is not available.

A related issue is whether the toxic response is reported in terms of the added metal in the diet or the total metal (i.e., whether the amount of trace elements in the control diet in the animal studies is included in the dose calculations). Risk assessors should carefully review the supporting documentation for toxicity values to determine precisely what is being reported and to account for any potential interactions among dietary metals. The assessor also should consider whether the study provided adequate levels of trace elements so that the observed toxicity is not secondary to some unrelated deficiency.

Dose-response assessments for some metals are based on data from human occupational studies. While derivation of the dose-response value (e.g., the RfC, RfD, or cancer slope factor) will have included some steps to extrapolate the occupational study data to environmental exposures (e.g., dosimetric and duration adjustments), the form of the chemical may merit consideration. For example, the occupational exposure will have involved a particular range of particle sizes, which may influence the response observed (U.S. EPA, 2002a).

Risk assessors should review RfDs derived for essential elements to ensure that they are not below required daily intakes. The RfD should not be below the general population RDA. This means that the risk assessor should give careful consideration to the appropriate size of uncertainty factors, which is often made easier by the frequent (although not uniform) availability of human data for relatively large and diverse populations. The only exception to the comparison between the RfD and nutritional requirements is that certain populations (e.g., pregnant women) may have higher nutritional requirements, while these levels could theoretically be toxic to other populations. In such cases, the risk assessor should be careful to avoid logical inconsistencies and to identify the sensitive population on which the RfD is based.

4.4. RISK CHARACTERIZATION

Risk Characterization is the final phase of the risk assessment process. It is the phase in which information from hazard characterization, dose-response assessment, and exposure assessment is considered together to determine the actual likelihood of risk to exposed

populations (NAS/NRC, 1994b). For example, inorganic As occurs naturally in food and water; thus, a risk characterization would integrate the currently accepted dose-response information for inorganic As with the exposure assessment information for a particular food or drinking water source, or for the national distribution of intake from food and water, to determine whether a potential problem exists. During Risk Characterization the uncertainties in the dose-response assessment, the uncertainties in the estimate of exposure derived for the scenario under evaluation, and the level of confidence in the overall determination of risk should be laid out. At the same time, Risk Characterization is the first phase in the risk management process, in which information from the characterization is integrated into the consequences of rule-making or risk management, such as consideration of cost, alternative solutions, political considerations, and community interactions.

Risk Characterization

Have the qualitative assessment, quantitative assessment, and key uncertainties regarding metals been presented in accordance with EPA guidelines?

Do conclusions fully reflect risks in relation to ambient concentrations, essentiality of metals, chemical speciation, and information on human variability in sensitivity?

Have assumptions and uncertainties been documented adequately?

Have available data on mechanisms of action and metal interactions been fully explored in developing the quantitative assessment?

Risk assessors should refer to guidance on Risk Characterization (U.S. EPA, 2000c) that identifies key goals and steps for a Risk Characterization. Each Risk Characterization should include three components: a qualitative summary of each section of the risk assessment, a numerical risk estimate, and a description of uncertainties. Since metal exposures often occur in the context of mixtures (either mixtures of metals of the same form, mixtures of different metal elements, or mixtures with organics), risk assessors should consult additional Risk Characterization tools developed for mixtures (U.S. EPA, 2000b, 1986). These guidelines specify that the characterization of risks from mixtures of metals (and other compounds) be based primarily on information about the types of interactions that might be present.

Risk assessors should include a discussion in the Risk Characterization of the sources of variability and uncertainty in the risk assessment process. This is particularly important for metals risk assessments given all the components above. These are in addition to the variability and uncertainties that are inherent in all risk assessments (e.g., animal-to-human toxicity extrapolations). Because information, knowledge, and tools are lacking for many of the metal-specific uncertainties, risk assessors should be particularly diligent in documenting whether these may result in an over- or underestimation of risk (i.e., result in a conservative risk estimate or not). It is likely that site-specific risk assessments will have fewer uncertainties than regional- or national-scale assessments because risk assessors have access to local data on key issues such as specific metal species, relative bioavailability, or current metal levels. For national or regional assessments, selection of ranges or specific numbers for these values will depend on the degree

of conservatism desired by the risk assessor and, therefore, should be clearly documented during the Risk Characterization phase.